American Journal of Infection Control 47 (2019) 323–333

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

State of the Science Review

The global and regional prevalence, burden, and risk factors for methicillin-resistant *Staphylococcus aureus* colonization in HIV-infected people: A systematic review and meta-analysis

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Key words:
MRSA
HIV
Meta-analysis
Prevalence
Risk factor

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is among the most important opportunistic pathogens in HIV+ patients, resulting in considerable morbidity and mortality.
Methods: The MEDLINE, Scopus, Web of Science, and EMBASE databases were comprehensively searched for studies that investigated the prevalence of MRSA colonization in HIV+ patients. We used a random effects model to calculate pooled prevalence estimates with 95% confidence intervals (CI) and analyzed data based on World Health Organization regions.
Results: Among 9,772 records identified, 69 were included in the meta-analysis, comprising 30,050 HIV+ patients from 21 countries. We estimated the pooled worldwide prevalence of MRSA in people living with HIV to be 7% (95% CI 5%-9%, 1,623/30,050), with the highest prevalence in Southeast Asia (16%, 95% CI 9%-24%) and the region of the Americas (10%; 95% CI 7%-13%) and lowest prevalence in the European region (1%; 95% CI 0%-1%). Globally, we estimated approximately 2,659,000 (95% CI 1,835,000-3,303,000) HIV+ patients with colonized MRSA. Potential risk factors for MRSA colonization in HIV+ patients included previous MRSA infection (OR, 7.5; 95% CI, 3.91-14.37), hospitalization in the past year (OR, 1.87; 95% CI 1.11-3.16), and use of antibiotics (OR, 2.52; 95% CI 1.39-4.58).
Conclusions: Our findings emphasize the importance of routine screening for MRSA among all HIV+ patients throughout the world, especially in regions that have a high burden of disease.

HIV continues to be a major public health problem worldwide. At the end of 2016, approximately 36.7 million people were infected with HIV, with 1.8 million new infections and 1.0 million deaths.[1] Opportunistic infectious agents are among the important causes of morbidity and death in HIV+ patients, mainly resulting from the diminished level of immunity due to destruction of CD4+ cells.[2] People living with HIV are at greater risk for opportunistic infections, particularly those caused by antibiotic-resistant organisms.[3]

Staphylococci, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), are among the most important opportunistic pathogens in HIV+ patients, causing considerable morbidity and death. Although MRSA can colonize in anyone, HIV+ patients are 6- to 18-fold more susceptible than healthy people, mainly owing to a compromised immune system.[4-6] MRSA in HIV+ patients results in greater morbidity and mortality rates, length of hospital stay, prolonged antibiotic administration, and medical costs.[7,8] Moreover, MRSA is related to other diseases including abscess, bacteremia, endocarditis, pneumonia, and pyomyositis.[7] Although several studies have evaluated

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Funding: This work was supported by the Health Research Institute in Babol University of Medical Sciences, Iran (grant number, 5280). This manuscript was approved by the Ethics Committee of Babol University of Medical Science (IR.MUBABOL.HRI.REC.1397.065).
Conflicts of interest: None to report.
Author contributions: P.S., S.M.R., and A.R. conceived the study. P.S. and S.M.R. initially searched the literature. All authors contributed to data extraction, analysis, and interpretation of the results. P.S., H.R.G., and A.R. drafted the manuscript. H.R.G. critically revised and edited the final version of the manuscript. All authors approved the final draft of the manuscript.
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https://doi.org/10.1016/j.ajic.2018.06.023
0196-6553/

demographic and geographic factors of MRSA colonization, the reasons for the higher risk in HIV+ patients are not completely known and are likely multifactorial.[7]

In the last 3 decades, a large number of studies have been performed on the prevalence of MRSA among HIV+ individuals; nevertheless there remains a gap in knowledge in many countries. Considering the clinical and economic importance of MRSA in HIV+ patients, a more comprehensive understanding on the prevalence of MRSA infection is needed. To address this need, in this study, we performed a systematic review and meta-analysis to evaluate the worldwide prevalence and burden and to determine potential risk factors for MRSA in people living with HIV.

METHODS

Search strategy and selection criteria

This systematic review and meta-analysis study was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[9] In this study, the prevalence of MRSA colonization among persons who are HIV+ was considered the main outcome of interest. Moreover, we evaluated the impact of different variables on the prevalence of MRSA colonization, including geographic area, sex, antibiotic use in the previous 6 months, use of trimethoprim-sulfamethoxazole (TMP-SMX), recent hospitalization, prior antiretroviral therapy, prior MRSA infection, and the use of highly active antiretroviral therapy (HAART). All observational (cross-sectional, cohort, or case-control) studies that evaluated the prevalence of MRSA colonization in HIV+ patients were included in the meta-analysis. We excluded studies if they did not have useable data on MRSA colonization, did not perform screening for MRSA colonization, were case-control or similar studies, were studies with no specified method for detection of MRSA, or were nonoriginal material such as reviews or letters.

Two independent investigators systematically searched the electronic databases of MEDLINE, Scopus, ISI (Web of Science), and EMBASE for relevant studies published up to January 2018, using the following search keywords: "human immunodeficiency virus," "immunodeficiency," "immunocompromised," "HIV," "AIDS," "*Staphylococcus*," "*Staphylococcus aureus*," "methicillin-resistant *Staphylococcus aureus*," "MRSA," "resistant bacterial infection," "prevalence," and "epidemiology," with the Boolean operators "OR" and/or "AND." The search was strengthened by reviewing reference lists of selected articles and related reviews. To further expand the search, we included the Google Scholar database using names of several countries in combination with the above-mentioned key words. We limited our search to human studies; however, there were no language, time, or geographic restrictions. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing our search strategy is shown in Figure 1.

Data extraction and quality assessment

Duplicate articles were removed, and titles and abstracts of all sources were screened to exclude those articles that clearly could not be included. The reviewers then assessed the full text of the remaining studies for detailed analysis of inclusion and exclusion criteria. Finally, data extraction was done from eligible studies for meta-analysis using Microsoft Excel. Any conflicts of opinion and disagreement were deliberated and resolved by consensus with a third reviewer. The Newcastle-Ottawa scale, for assessment of different aspects of

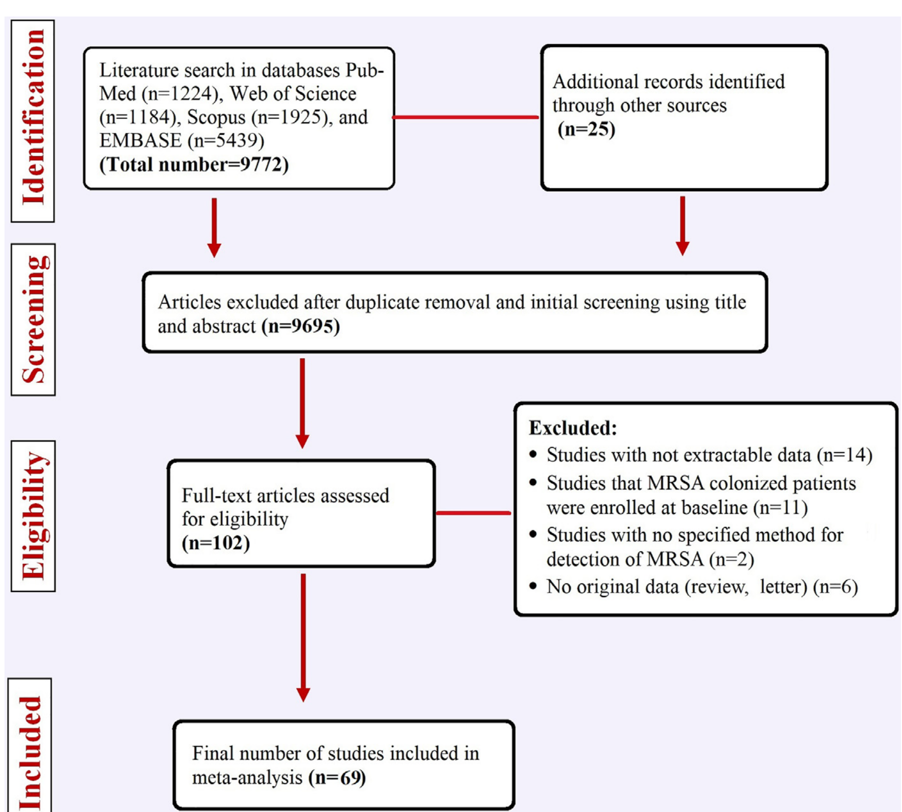

Fig 1. Flow chart of the study selection process showing inclusion and exclusion of studies identified.

Table 1
Main characteristics of selected studies reporting the prevalence of methicillin-resistant *Staphylococcus aureus* colonization in HIV+ patients

WHO regions/references	Country	Type of sample	Study design	Positive sample/ total samples	Dominant strain	Main risk factors	Quality score
Region of Americas							
Raviglione et al (1990)[13]	USA	N	Case-control	3/64	NR	NS	5
Klein (1997)[14]	USA	N, A, W	Cross-sectional	0/33	NR	NS	4
Padoveze et al (2001)[15]	Brazil	N	Cohort	60/178	NR	H	5
Miller et al (2003)[16]	USA	N	Cohort	8/193	SCC-mec-type IV	NS	4
Mathews et al (2005)[17]	USA	All	Cohort	126/3455	NR	UA, U TMP-SMX, CD, HIVPVL	4
Hidron et al (2005)[18]	USA	N	Cross-sectional	14/81	USA300/ SCC-mec-type IV	UA, H, HIVI, PI, STI	5
Crum-Cianflone et al (2007)[6]	USA	N, W	Retrospective	31/435	NR	UA, LC, HIVPVL, HOS	5
Cenizal et al (2008)[19]	USA	N, A	Cross-sectional	15/146	USA300/ SCC-mec-type IV	LC, NAC, PSI	5
Padoveze et al (2008)[20]	Brazil	N	Cohort	0/111	NR	NS	5
Farley et al (2008)[21]	USA	N	Cross-sectional	4/30	USA300	NS	4
Krucke et al (2009)[22]	USA	W	Retrospective	66/113	NR	NS	5
Antoniou et al (2009)[23]	USA	N, P	Cohort	4/298	USA300/ SCC-mec-type IV	NS	4
Madariaga et al (2009)[24]	USA	N, PG	Cross-sectional	2/100	NR	NS	4
Szumowski et al (2009)[25]	USA	N, W, PA	Cohort	30/795	NR	NS	5
Shet et al (2009)[26]	USA	N, A	Case-control	18/107	SCC-mec-type IV, USA300, Spa-type 1	UA	4
Mermel et al (2010)[27]	USA	N	Cohort	5/161	USA300	NS	5
Mermel et al (2010)[27]	USA	N	Cohort	78/494	USA300	NS	5
Ramsetty et al (2010)[28]	USA	N	Retrospective	72/900	USA300	UA, LC	5
Schechter-Perkins et al (2011)[29]	USA	N, G, PR, T, W, S, OPH	Cross-sectional	4/11	USA300	NS	5
Crum-Cianflone et al (2011)[30]	USA	N, A, G, P, PR, T	Cross-sectional	22/550	USA300, SCC-mec-type IV	PI	5
Alexander et al (2011)[31]	USA	N	Cohort	1/15	NR	NS	4
McAllister et al (2011)[32]	USA	N, G	Cohort	128/600	USA300, USA500/ Iberian	NS	5
Popovich et al (2012)[4]	USA	N	Cross-sectional	50/458	USA300	I, HE, PI, STI	4
Siberry et al (2012)[33]	USA	N	Cross-sectional	14/1813	NR	NHB, HIVPVL,MHIV	
Farley et al (2013)[34]	USA	N, A, W	Cross-sectional	63/498	USA300	H, AB	4
Popovich et al (2013)[35]	USA	N, A, G, P, PR, T, W	Cross-sectional	76/374	USA300	I, AG, MS	4
Peters et al (2013)[36]	USA	N, G	Cross-sectional	79/600	USA300	LC, AB, PI, HOS, UA	5
Reinato et al (2013)[37]	Brazil	N	Cross-sectional	10/169	NR	NS	5
Everett et al (2014)[38]	USA	N	Case-control	10/68	NR	NS	4
Vyas et al (2014)[39]	USA	N	Retrospective	26/130	NR	LC, UID, HIVPVL	5
Farley et al (2015)[40]	USA	N	Cross-sectional	77/500	NR	NS	4
Hidalgo et al (2015)[41]	Colombia	N, A	Cross-sectional	3/283	USA300-LV, SCC-mec-type IV	NS	5
Befus et al (2016)[42]	USA	N, OPH	Cross-sectional	9/117	Spa types t571, Spa types t064	NS	5
Vieira et al (2016)[43]	Brazil	N	Case-control	32/117	Spa types t002/ST5 and t318/ST30	C	4
Farley et al (2017)[44]	USA	N, P, V	Cross-sectional	28/77	NR	H, AB, UID	4
European region							
Weinkel et al (1992)[45]	Germany	N, T	Case-control	0/136	NR	NS	5
Sissolak et al (2002)[46]	Austria	N	Cross-sectional	0/47	NR	NS	4
Tumbarello et al (2002)[47]	Italy	B	Cohort	41/4671	NR	H, LC, UA	5
Drapeau et al (2007)[48]	Italy	W, B, S, R	Retrospective	28/5257	NR	LC, H, PIP	5
Seybold et al (2009)[49]	Germany	N	Cross-sectional	2/100	NR	NS	5
Giuliani et al (2010)[50]	Italy	N	Cross-sectional	2/104	NR	NS	4
Oliva et al (2013)[51]	Italy	N	Retrospective	2/131	NR	NS	5
Joore et al (2013)[52]	Netherlands	N, T, PA	Cross-sectional	1/42	NR	NS	4
Imaz et al (2015)[53]	Spain	N, PH	Cross-sectional	3/190	ST146/ST125, SCC-mec-type IV	NS	4
Western pacific region							
McDonald et al (2003)[54]	Taiwan	N	Cohort	9/162	NR	LC, UA	5
Villacian et al (2004)[55]	Singapore	N	Cross-sectional	6/195	NR	UA, LC, U TMP-SMX, H	5
Chow et al (2012)[56]	Singapore	N, A, G, PA, T, W	Cross-sectional	10/96	NR	NS	5
Kyaw et al (2012)[57]	Singapore	N, A, G, PA, T	Case-control	15/296	NR	UA, LC, H, PPD	5
Mohd-Nawi et al (2012)[58]	Malaysia	N, A, T, S	Cross-sectional	1/130	NR	NS	4
Wu et al (2017)[59]	Taiwan	N	Cross-sectional	20/457	SCC-mec type IV, SCC-mec type V, ST59	I	5
Mohd-Zain et al (2017)[60]	Malaysia	N, A, S, T	Cross-sectional	1/129	NR	NS	5
South-East Asia Region							
Chacko et al (2009)[61]	India	N	Cross-sectional	8/60	NR	H	4

(*continued*)

Table 1 (*Continued*)

WHO regions/references	Country	Type of sample	Study design	Positive sample/ total samples	Dominant strain	Main risk factors	Quality score
Kumar et al (2013)[62]	India	N	Cross-sectional	26/142	NR	UA, LC	5
Kotpal et al (2016)[63]	India	N	Case-control	3/50	NT	AI	4
Alexander et al (2017)[64]	India	N	Cohort	49/194	NR	UA, PD, AV	4
Eastern Mediterranean Region							
Hassanzadeh et al (2015)[65]	Iran	N	Cross-sectional	23/180	NR	NS	4
Saeed et al (2015)[66]	Bahrain	N	Retrospective	2/194	NR	NS	5
Naderpour et al (2015)[67]	Iran	N	Cross-sectional	4/155	NR	NS	3
Africa							
Cotton et al (2008)[68]	South Africa	NPH	Cross-sectional	34/203	NR	UTMP-SMX	5
Abraham et al (2009)[69]	Nigeria	U	Cross-sectional	6/111	NR	NS	5
Ouko et al (2010)[70]	Kenia	W, B, CSF, U, R	Cross-sectional	21/220	NR	PSI	4
Heysell et al (2011)[71]	South Africa	N	Cohort	9/44	NR	LC	3
Olalekana et al (2012)[72]	Nigeria	N	Cross-sectional	60/374	NR	NS	5
Tibebu et al (2015)[73]	Ethiopia	N	Cross-sectional	24/400	NR	NS	4
Gebremedhn et al (2016)[5]	Ethiopia	N, T	Cross-sectional	6/249	NR	NS	5
Olalekan et al (2016)[74]	Nigeria	N	Cross-sectional	20/187	NR	LC	5
Sampane-Donkor et al (2017)[75]	Ghana	NPH	Cross-sectional	4/118	NR	NS	5
Adesida et al (2017)[76]	Nigeria	Blood	Cross-sectional	0/86	NR	NS	5
Reid et al (2017)[77]	Botswana	N	Cross-sectional	13/404	NR	LC, AS, E, RL	4
Bebell et al (2016)[78]	Uganda	N	Cross-sectional	4/166		NS	5

A, axilla; *AB*, abscess; *AG*, age; *AI*, alcohol intake; *AS*, asthma; *AV*, antiretroviral; *B*, blood; *C*, crowding; *CD*, CD4 cell count; *CSF*, cerebrospinal fluid; *E*, eczema; *G*, groin; *H*, hospitalization; *HE*, Hispanic ethnicity; *HIVI*, HIV infection; *HIVPVL*, HIV plasma viral load; *HMH*, household member hospitalized; *HOS*, history of syphilis; *I*, incarceration; *LC*, low CD4+ count; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MS*, male sex; *MHIV*, Maryland HIV care site; *N*, nares; *NAC*, no antibiotics currently; *NHB*, non-Hispanic black; *NPH*, nasopharynx; *NR*, not reported; *NS*, no significance; *NT*, nontypeable; *NTH*, nothing; *OPH*, oropharynx; *P*, perineum; *PA*, perianal; *PD*, percutaneous device; *PG*, perigenital; *PH*, pharyngeal; *PI*, prior MRSA infection; *PIP*, previous invasive procedures; *PPD*, presence of percutaneous device; *PR*, prerectal; *PSI*, prior staphylococcal infection; *R*, respiratory; *RL*, rural living; *S*, skin; *SCC-mec*, staphylococcal cassette chromosome mec; *STI*, skin or soft-tissue infection; *T*, thorax; *TMP-SMX*, trimethoprim/sulfamethoxazole; *U*, urine; *UA*, use antibiotics; *UID*, use injection drug; *UPWR*, use of prison weight room; *UTMP-SMX*, use of trimethoprim-sulfamethoxazole; *W*, wound.

population-based studies of prevalence, was used to determine the methodologic quality of included studies.[10,11]

Data analysis

Pooled MRSA prevalence at a 95% confidence interval was estimated using a random effect model. Heterogeneity between studies was examined by Cochran's Q, the I^2 statistics test, and a Galbraith plot. I^2 ranges between 0% and 100% and values ≥50% were considered heterogeneous. To address the sources of heterogeneity, metaregression and subgroup analyses were performed using the following variables: (1) geographic region, based on continents and World Health Organization (WHO) regions; (2) a human development index (HDI); (3) the time period of study; (4) the publication year; and (4) the mean age of participants. Moreover, to calculate the global burden of MRSA in HIV+ patients, we followed a recently published study in *Lancet HIV*[12] and used data from WHO showing the number of people living with HIV in 2016.[1] We then multiplied this number by our calculated percentage of HIV+ people with MRSA (with a 95% CI).

Assessing publication bias in prevalence studies is not routine and logical, because the aim of these studies is not to examine the association between exposures and outcomes.[13] However, publication bias related to different risk factors was evaluated by applying funnel plots and Egger's regression analyses. All statistical analyses were done using the STATA version 13 (STATA Corp., College Station, TX), and $P < .05$ was considered significant.

Role of funding source

The funders of this study had no role in study design or in other parts of the study. The corresponding authors had access to the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study characteristics

A total of 9,772 records were identified from our literature search. After initial title and abstract review and duplicate removal, 102 original, full-text research articles were reviewed. Of these, 33 articles were excluded based on the stated inclusion and exclusion criteria. Finally, 69 eligible articles including 30,050 individuals were included in the meta-analysis.[4-6,13-79] The included studies covered all 6 WHO regions (34 from the region of the Americas [n = 14,370 participants], 12 from the African region [n = 2,562 participants], 9 from the European region [n = 10,678 participants], 7 from the Western Pacific region [n = 1,465 participants], 4 from the Southeast Asia region [n = 446 participants], and 3 from the Eastern Mediterranean region [n = 529 participants]), representing 21 countries. The country with the highest number of reports was the United States (29 studies, 13,512 participants), Five studies were of children (n = 2,651 participants). Considering income level, 38 studies (n = 24,190 participants) were from countries with a high level of income, 17 (n = 3,099 participants) were from countries with a moderate level of income, and 14 (n = 2,761 participants) were from low-income countries. Most of the studies followed a prospective or cross-sectional design and used culture methods to identify MRSA. Among the included studies, 21 analyzed molecular characteristics of isolated MRSA. These data showed that the subtypes USA300 or SCC-mec-type IV were the predominant isolates recovered from HIV+ patients (Table 1). The main features of studies included in this meta-analysis are presented in Table 1.

Results of the meta-analysis

As shown in Table 1 and Figure 2, the estimated prevalence of MRSA in patients with HIV infection ranged from 0.0% to 58%. The worldwide pooled MRSA prevalence estimate among HIV+ patients was 7% (95% CI 5%-9%; 1,623/30,050), and heterogeneity was

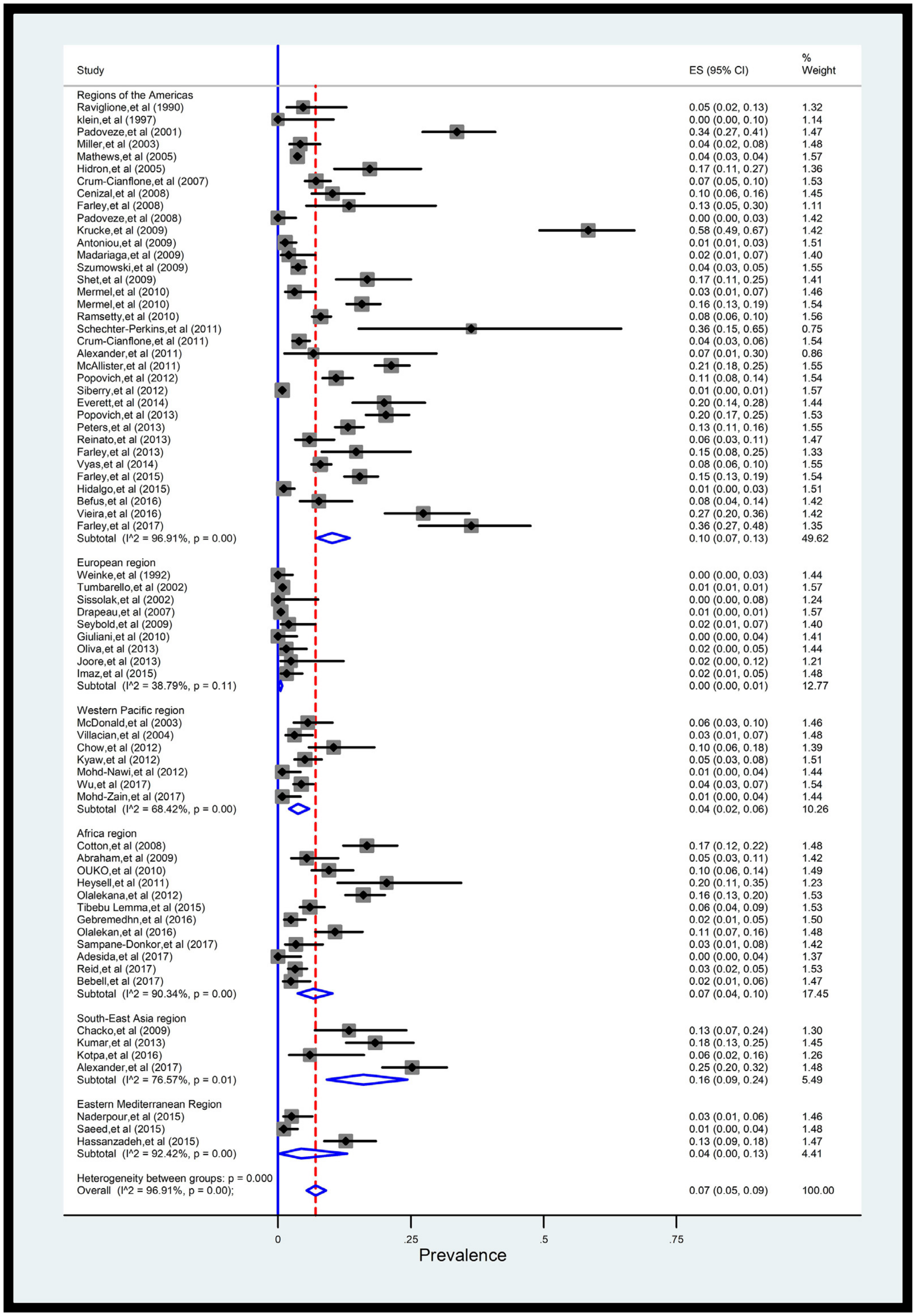

Fig 2. Forest plots for random-effects meta-analysis of methicillin-resistant *Staphylococcus aureus* colonization in HIV patients based on prevalence in different WHO regions.

substantial (I^2 = 96.9%, $P < .001$; Fig 2). The WHO regions with the highest MRSA prevalence were Southeast Asia (16%, 95% CI 9%-24%, 86/446) and the region of the Americas (10%, 95% CI 7%–13%, 1,168/14,370); the lowest prevalence was found in the European region, where MRSA prevalence was 1% (95% CI 0%-1%, 77/10,678). The pooled MRSA prevalence in other WHO regions were African region 7% (95% CI 4%-10%; 201/2,562), Western Pacific region 4% (95% CI 2%-6%; 62/1,465), and Eastern Mediterranean region 4% (95% CI 0%-13%; 29/529) (Fig 2). The MRSA prevalence based on different continents are shown in Supplementary Figure 1. No data were available for the region of Oceania. Because approximately one-half of the included studies (29/70) were from the United States, we performed a separate

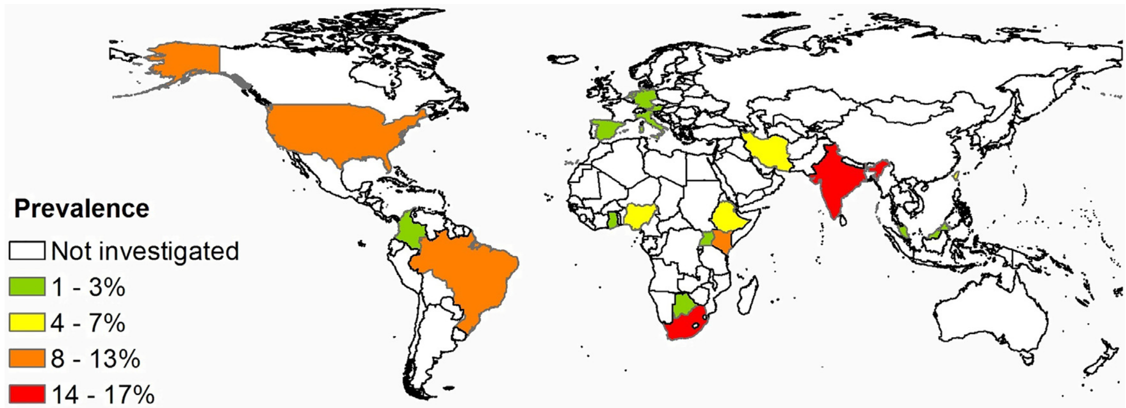

Fig 3. Distribution of methicillin-resistant *Staphylococcus aureus* colonization in HIV patients in different countries using geographic information system (GIS).

analysis for this country. Results of this analysis (Supplementary Fig 2) showed that MRSA prevalence was 10% (95% CI 7%-14%; I^2 = 96.1%). A geographic information system map summarizing the MRSA prevalence among HIV+ patients in various countries is shown in Figure 3.

In 1 subgroup analysis, the pooled MRSA prevalence in children with HIV (9%; 95% CI 2%-20%; 108/2,651) was slightly higher than in adult HIV+ patients (7%; 95% CI 5%-9%) (Supplementary Fig 3). In other subgroup analyses, by income level and HDI, we observed limited differences in MRSA prevalence. The pooled MRSA prevalence in countries with high, moderate, and low levels of income were 7% (95% CI 5%-10%; 1,140/24,190), 7% (95% CI 3%-11%; 239/3,099), and 7% (95% CI 4%-11%; 244/2,761), respectively (Supplementary Fig 4). The pooled MRSA prevalence in countries with high, moderate, and low levels of HDI is shown in Supplementary Figure 5.

Regarding risk factors associated with MRSA colonization, we found that individuals with a history of previous MRSA infection (odds ratio [OR], 7.5; 95% CI 3.91-14.37), a history of hospitalization within the previous year (OR, 1.87; 95% CI 1.11-3.16), and those who used antibiotics in the previous 6 months (OR, 2.52; 95% CI 1.39-4.58) were more likely to be colonized by MRSA than were other patients (Fig 4 A-C). Other risk factors were not significantly associated with an increased risk of MRSA colonization (Table 2 and Supplementary Figs 6-9). Meta-regression results showed that time period of the study, publication year, and mean age of participants were not sources of heterogeneity (Supplementary Figs 10 and 11). An interesting finding was the trend of increasing MRSA prevalence among HIV+ patients over the course of time included in our analysis (Fig 5). Egger's test did not identify any significant publication bias (Supplementary Fig 12).

To calculate the worldwide burden of MRSA in persons who are HIV+, we used the global prevalence calculated here (7%; 95% CI 5-9) and data on the number of HIV+ people in different WHO regions from the 2016 data of the WHO report.[1] From this, we estimated that approximately 2,659,000 (1,835,000-3,303,000) HIV+ people worldwide were colonized with MRSA. Our estimates demonstrated that countries in the African region, which has a large proportion of HIV+ patients, has the largest number of people with MRSA colonization 1,792,000 (1,024,000-2,560,000), accounting for approximately 70% of cases of HIV-MRSA coinfection worldwide (Table 3).

DISCUSSION

S aureus is among the most common pathogens in hospital-acquired infections and also in patients with a suppressed immune system. It is considered a major threat to public health, especially when caused by methicillin-resistant strains of *S aureus*.[80] There is a higher mortality rate (OR,1.93; 95% CI 1.54-2.42) associated with MRSA strains than with methicillin-sensitive *S aureus* strains.[81]

Results of our meta-analysis showed that 7% of people living with HIV are colonized with MRSA, a rate that is significantly higher than in healthy persons (0.2%-3.5%).[82] A previous meta-analysis showed that the pooled MRSA colonization rate among community members was 1.3% (95% CI 1.04%-1.53%).[83] Moreover, pooled MRSA prevalence among HIV+ patients in our study was roughly similar to other high-risk individuals such as patients undergoing hemodialysis (6.2%; 95% CI 4.2%-8.5%) and patients admitted to a general intensive care hospital setting (7.0%; 95% CI 5.8%-8.3%), although this prevalence rate was lower than those reported for burn patients (13%-80%).[84,85] In our subgroup analysis, results showed a prevalence of 9% for MRSA in children with HIV, whereas this rate in healthy children is 1%-3%.[86,87]

Our results indicated that prevalence of MRSA in HIV+ patients has substantial geographic variability, with the lowest prevalence in the European region and the highest prevalence in some countries in the Americas and the Southeast Asia region. Similar findings were observed in 2 previous meta-analysis studies in high-risk populations.[88,89] This variability in geographic prevalence of MRSA colonization could be explained by different rates of antibiotic use, different infection control programs, and different cultural practices among the countries studied.[88,90] Another interesting result in this study was the increase in prevalence of MRSA in HIV+ patients over the course of time, which is similar to MRSA infection in patients undergoing hemodialysis and also patients in intensive care,[88,89] although it is in contrast to a relatively stable or, in some studies, decreasing trend of MRSA nasal carriage in healthy people and the general hospital population.[91,92]

Regarding risk factors, we found that prior hospitalization, prior MRSA infection, and prior use of antibiotics were potential risk factors for MRSA colonization among persons who are HIV+. More frequent interaction with other patients, contact with materials contaminated with MRSA, and contact with infected health care staff could explain a higher prevalence of MRSA in hospitalized patients. Prior MRSA infection as a risk factor may be partially explained by persistent colonization in nasal or other sites.[20,93,94] Furthermore, frequent exposure to β-lactam antibiotics is a well-known cause for development of antimicrobial resistance in staphylococci and other bacteria.[95,96] Several previous studies reported that other risk factors for MRSA colonization include substance abuse, high-risk sexual practices, having a sexual partner with a known skin infection, male sex, incarceration history, lower CD4 counts, high viral load, and a lack of cotrimoxazole prophylaxis.[41,97-100] Our results showed that HIV+ patients

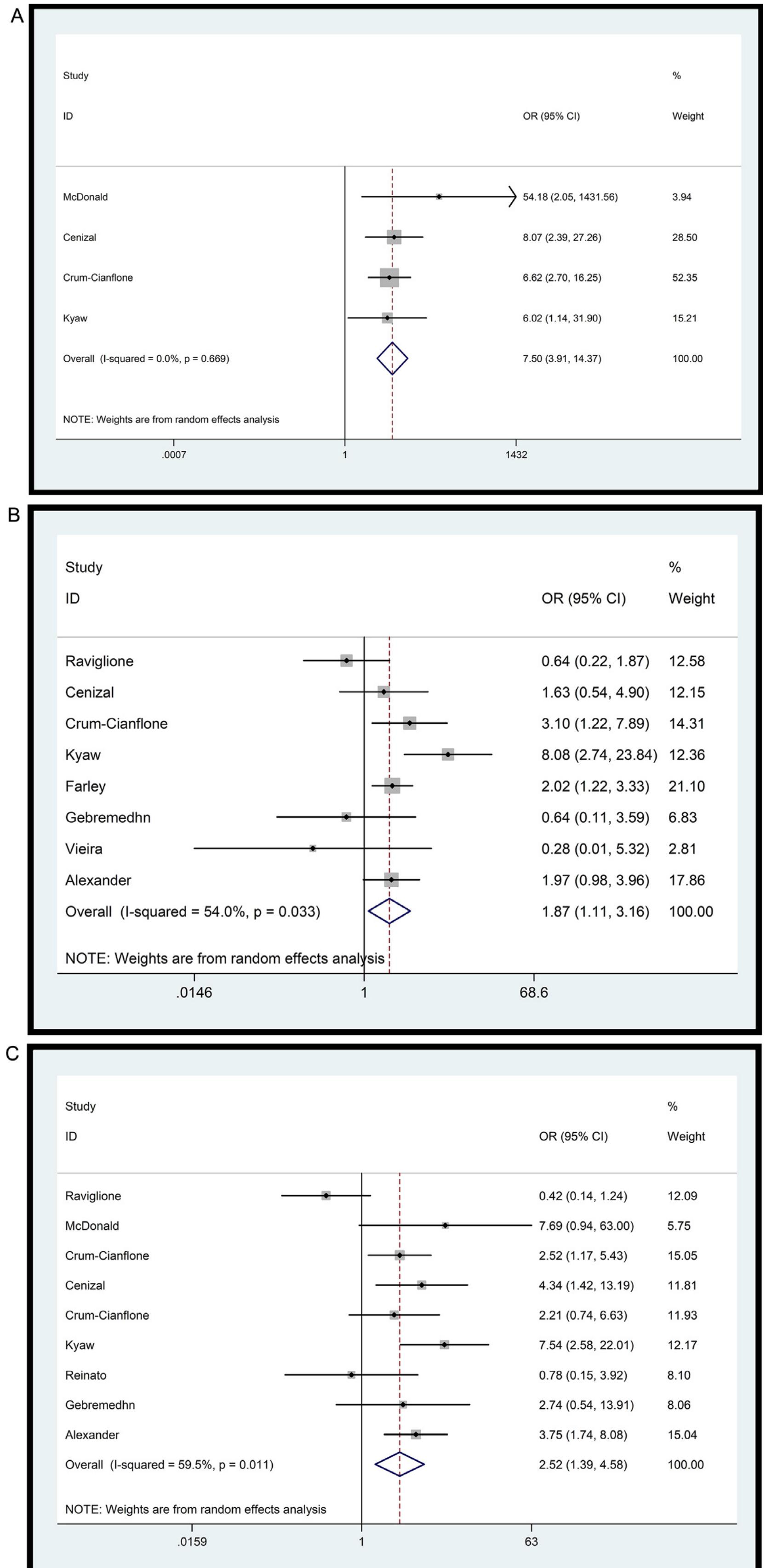

Fig 4. Forest plots for pooled odds ratios (ORs) of methicillin-resistant *Staphylococcus aureus* (MRSA) co-infection with respect to potential significant risk factors; (A), having a previou MRSA; infection (B), hospitalization in the past year; (C), use of antibiotics in the past 6 months. Patients without previous MRSA infection and antibiotic use are considered as reference categories to estimate the OR.

Table 2
Risk factors associated with MRSA colonization in people with HIV

Variables (no. of studies)	No. of HIV+ patients	Number (%) of MRSA positive	OR (95% CI)	Heterogeneity				Publication bias *P* value
				χ^2	df	I^2 (%)	*P* value	
Sex (13)				16.78	12	28.5	0.15	.08
Women	808	75 (9.2)	1					
Men	3127	229 (7.3)	1.04 (0.64-1.69)					
Antibiotics past 6 months (9)				19.76	8	59.5	0.01	.77
No	1301	96 (7.3)	1					
Yes	934	94 (10)	2.59 (1.32-4.58)					
Use of TMP-SMX (9)				11.24	8	28.8	0.18	.48
No	2083	177 (8.4)	1					
Yes	704	74 (10.5)	1.29 (0.8-2.1)					
Previous MRSA infection (4)				1.56	3	0.00	0.66	.16
No	1069	43 (4)	1					
Yes	85	18 (21.1)	7.5 (3.91-14.37)					
Receiving HAART therapy (7)				10.64	1	43.6	0.1	.32
No	659	73 (11)	1					
Yes	2118	191 (9)	0.69 (0.45-1.06)					
Use of antiretroviral (4)				8.53	3	64.8	0.036	.8
No	238	35 (14.7)	1					
Yes	560	34 (6)	0.88 (0.26-2.97)					
Hospitalization in past year (5)				15.23	7	54.0	0.03	.9
No	1514	153 (10.1)	1					
Yes	601	98 (16.3)	1.87 (1.11-3.16)					

HAART, highly active antiretroviral therapy; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *OR*, odds ratio; *TMP-SMX*, trimethoprim-sulfamethoxazole.

undergoing HAART or antiretroviral therapy have lower risk of MRSA colonization, although it was not significant. It has been stated that TMP-SMX has antistaphylococcal activity, although our results showed that patients receiving TMP-SMX have higher, but not significant, odds of MRSA colonization compared with patients not receiving TMP-SMX. It could be explained by the fact that patients who receive antiretroviral therapy or TMP-SMX prophylaxis might have a lower CD4 count than those who do not receive therapy, and this may increase their risk of MRSA colonization.[101] Because the studies included in our meta-analysis used diverse cutoffs or provided mean values of CD4 and viral load without providing raw data, we were unable to estimate the impact of these factors on the prevalence of MRSA in HIV+ patients.

During the literature search performed for this meta-analysis, we noticed another meta-analysis published in this issue.[101] This other publication included 32 studies (46% of those included in our meta-analysis) and 6,558 HIV+ individuals (approximately 22% of individuals in our meta-analysis). To avoid duplication of reporting, we have not included incarceration as a risk factor in our analysis. The previous meta-analysis [101] demonstrated that previous or current incarceration was significantly related (RR: Relative Risk, 1.77; 95% CI 1.26-2.48) with a higher risk for MRSA colonization in HIV+ patients.

The strengths of the current meta-analysis included the comprehensive literature search, rigorous methodology including independent review by 2 authors, the resulting large sample size of HIV+ individuals, subgroup analyses, and metaregression considering sex, age, income, and HDI levels of countries, geographic location, as well as an assessment of potential risk factors. Our meta-analysis was limited by the fact that, in spite of our comprehensive search, it is possible that all relevant studies were not identified, including some published in languages other than English and in local journals. Also, because the majority of studies included here used culture methods to identify MRSA infections, with a lower sensitivity compared with molecular methods, the present results might underestimate the prevalence and burden of MRSA in HIV+ individuals. Furthermore, different culture methods might have different sensitivities and specificities, which may limit the accuracy of the pooled estimate. Another limitation for this study is that relevant articles were available for only 21 countries, mainly owing to a lack of published reports from the other countries. A large number of included studies were from the United States, and reports were only available from 5 African countries, a region that has the highest proportion of HIV+ individuals and lowest-income countries. In some countries, only 1 report was available, and there were no reports from China or the region of Oceania. Notwithstanding these limitations, we expect that HIV+ patients in countries with missing data have similar prevalence or burden of MRSA as the pooled mean prevalence in the same regions. Despite these aforementioned limitations, the meta-analysis

Table 3
Global burden of MRSA colonization in people with HIV

WHO regions	Estimated number of HIV-infected individuals*	Prevalence (95% CI) of MRSA co-infection	Estimated number of HIV-infected individuals with MRSA
Region of the Americas	3,300,000	10% (7-13)	330,000 (231,000–429,000)
European Region	2,400,000	1% (0-1)	24,000 (0–24,000)
Western Pacific Region	1,500,000	4% (2-6)	60,000 (30,000–90,000)
African Region	25,600,000	7% (4-10)	1,792,000 (1,024,000–2,560,000)
Southeast Asia Region	3,500,000	16% (9-24)	560,000 (315,000–840,000)
Eastern Mediterranean Region	360,000	4% (0-13)	14,400 (0–46,800)
Global (WHO)	36,700,000	7% (5-9)	2,569,000 (1,835,000–3,303,000)

MRSA methicillin-resistant *Staphylococcus aureus*; *WHO*, World Health Organization. *Estimates of the number of HIV-infected individuals in each region were obtained from 2016 data of the WHO report.[1]

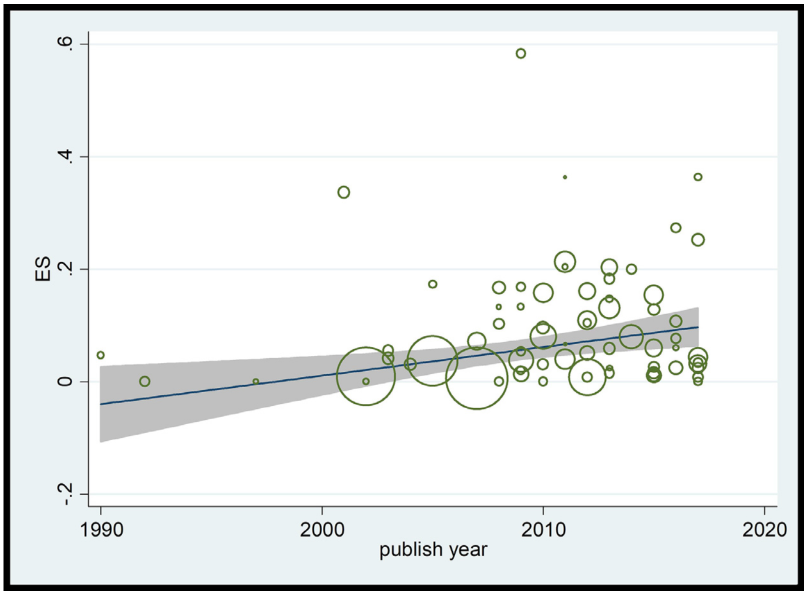

Fig 5. Metaregression regarding the effects of time of publication on the prevalence of methicillin-resistant *Staphylococcus aureus* MRSA in people living with HIV.

and interpretation presented here provide a comprehensive overview and further the understanding of the prevalence of MRSA in people living with HIV on the global level. We suggest additional studies in different parts of the world, especially in areas or countries lacking data on the prevalence of MRSA in HIV+ patients.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajic.2018.06.023.

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